
(12) **UK Patent Application** (19) **GB** (11) **2 007 091 A**

- (21) Application No **7834601**
(22) Date of filing **25 Aug 1978**
(23) Claims filed **25 Aug 1978**
(30) Priority data
(31) **52/133216**
(32) **7 Nov 1977**
(33) **Japan (JP)**
(43) Application published
16 May 1979
(51) **INT CL⁴**
A61K 47/00
(52) Domestic classification
A5B 210 21Y 241 244
245 246 247 24Y 27X 27Y
281 28Y 301 30Y 327 32Y
351 35Y 361 36Y 390 39X
410 41Y 482 48Y 491 49Y
503 50Y 511 513 51Y 542
54Y 551 55Y 576 57Y 616
61Y J
(56) Documents cited
GB 1471099
GB 1414182
GB 1316556
(58) Field of search
A5B
(71) Applicants
Toko Yakuhin Kogyo
Kabushiki Kaisha, No.
12-23 Honjyo - nishi 2 -
chome, Oyodo - ku,
Osaka, Japan
(72) Inventors
Takuzo Kamishita
Kazuhiko Kamishita
(74) Agents
Venner, Shipley & Co.

(54) Ophthalmic composition

(57) An ophthalmic composition in the form of a gel comprises an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance and an ophthalmic drug admixed therewith, the gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

SPECIFICATION

Ophthalmic preparations and process for producing the same

.5

The present invention is concerned with novel ophthalmic preparations and with the preparation thereof.

Eye lotions and ophthalmic ointments are widely used. Eye lotions, which usually contain purified water as the base ingredient, do not spread easily over the cornea or become diluted with tears when applied to the eye so that a large amount of the lotion falls off the eyelids. Thus, difficulties have been encountered in ensuring full retention of the medicinal ingredient of eye lotions on the eyelids or absorption thereof by the body.

Ophthalmic ointments which contain petroleum jelly or a mixture of petroleum jelly and liquid paraffin or purified lanolin as the base ingredient are not hydrophilic and are, therefore, liable to be dislodged from the eyelids and be unable effectively to adhere to the cornea and the mucous membrane of the eye. Accordingly, they have the drawback of failing fully to release the active ingredient therefrom, permitting only a small amount thereof to reach the affected part for absorption. Furthermore, ophthalmic ointments have the added drawback that the oily base ingredient gives the eyelids an unpleasant feel due to stickiness when the ointment is applied.

We have carried out intensive research to overcome these drawbacks and to provide highly effective ophthalmic preparations which enable the mucous membrane of the eye, the cornea and the like fully to absorb ophthalmic drugs and have found that preparations incorporating a carboxyvinyl polymer provide a specified viscosity product with outstanding effects.

Thus, according to the present invention, there is provided an ophthalmic composition in the form of a gel comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance and an ophthalmic drug admixed therewith, the gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C. If desired, the preparation can also contain sodium chloride.

The carboxyvinyl polymers used according to the present invention are hydrophilic polymers which can be obtained by the polymerisation or copolymerisation of acrylic acid. Examples of such polymers include those commercially available under the Registered Trade Mark "Carbopol" 934, 940 and 941 and manufactured by B. F. Goodrich Chemical Co. U.S.A.

Carboxyvinyl polymers contain free carboxy groups. Aqueous solutions of such polymers are acid and form a uniform gel when neutralised with a base. Examples of water-soluble basic substances which can be used according to the present invention for neutralising carboxyvinyl polymers include organic amines, for example alkylamines, such as methylamine, ethylamine and propylamine; dialkylamines, such as dimethylamine, diethylamine and dipropylamine; trialkylamines, such as trimethylamine, triethylamine and tripropylamine;

alkanolamines, such as methanolamine, ethanolamine and propanolamine; dialkanolamines, such as dimethanolamine, diethanolamine, dipropanolamine and dibutanolamine; trialkanolamines, such as trimethanolamine, triethanolamine, tripropanolamine and tributanolamine; and trimethylolaminomethane. Inorganic bases, such as aqueous solutions of ammonia and alkali metal hydroxides, can also be

used. Carboxyvinyl polymers when neutralised, give gels of substantially the same viscosity, irrespective of the kind of the basic substance used.

Preferably, the neutralisation of the carboxyvinyl polymers with the water-soluble basic substances is generally so adjusted that the resulting composition in the form of a gel has an approximately neutral pH, i.e. of 5 to 8. It is advantageous for the composition to have a pH value which is most favourable for the stability of the drug to be incorporated therein.

Accordingly, the gel composition of the present invention should be adjusted to a pH of 5 to 8.

According to this invention, ophthalmic drugs can be used regardless of whether they are soluble or insoluble in water. When water-insoluble drugs are used, they render the resulting gel composition turbid but do not precipitate in the composition so that the composition is readily applicable. However, an auxiliary dissolving agent can be used to render the composition transparent or absorbable by the body more effectively. Alternatively, the ophthalmic drug can first be dissolved in a water-soluble organic solvent and then incorporated into the composition. Examples of such water-soluble organic solvents include propylene glycol, polyethylene glycols having molecular weights of 300 to 400 and the like, among which propylene glycol, which is widely usable, is especially preferred. Furthermore, water-soluble basic substances can be used also as solvents. Examples of auxiliary dissolving agents include non-ionic surfactants, including fatty acid esters of polyoxyethylene sorbitan, such as polyoxyethylene sorbitan monopalmitate and polyoxyethylene sorbitan monostearate; polyoxyethylene alkyl ethers, such as polyoxyethylene lauryl ether, polyoxyethylene cetyl ether, polyoxyethylene stearyl ether, polyoxyethylene oleyl ether and polyoxyethylene behenyl ether; and benzyl alcohol.

Ophthalmic drugs which can be used according to the present invention include those which are non-ionic and stable in the preparations, i.e. in aqueous media. Examples of ophthalmic drugs which can be used in the gel preparations of the present invention include prednisolone, cortisone, hydrocortisone, hydrocortisone acetate, methyl prednisolone, cortisone acetate, cortisone caproate, dexamethasone, betamethasone, betamethasone valerate, betamethasone benzoate, dexamethasone acetate, dexamethasone valerate, flumethasone, flucinolone acetonide, fluciclonide, flumethasone, prednisolone acetate, methylprednisolone acetate, triamcinolone, triamcinolone acetonide and like adrenocortical hormones and derivatives thereof; chloramphenicol, tetracycline, oxytetracycline, chlortetracycline, penicillin and like antibiotics; vitamin B₂, vitamin B₆, vitamin B₁₂, vitamin A, vitamin E,

vitamin D and like vitamins; boric acid, acrinol, azulene, flavine adenine dinucleotide, allantoin, glutathione, sulpha drugs and the like.

The present invention also provides a process for preparing the ophthalmic composition, wherein an aqueous solution of a carboxyvinyl polymer is uniformly mixed with a water-soluble basic substance and an ophthalmic drug is added to the solution to give a gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

According to one embodiment of this process, the ophthalmic drug is dissolved or dispersed in the aqueous carboxyvinyl polymer solution and the resulting solution or dispersion is uniformly mixed with the water-soluble basic substance.

According to another embodiment of this process, the aqueous carboxyvinyl polymer solution is uniformly mixed with the water-soluble basic substance and the resulting mixture is uniformly mixed with the ophthalmic drug or with a solution thereof.

According to another process for preparing the new ophthalmic composition, sodium chloride or an aqueous solution thereof is added to an aqueous solution of a carboxyvinyl polymer or to a base composition in the form of a gel prepared by adding a water-soluble basic substance to the polymer solution or to an ophthalmic composition in the form of a gel prepared by adding an ophthalmic drug to the base composition, followed by uniformly mixing the resulting mixture to give a gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

Gels with a viscosity of less than 1,000 centipoises flow readily like conventional aqueous eye lotions and will flow out of the body as such or contained in tears when applied and thus are undesirable. If the viscosity exceeds 100,000 centipoises, the gels are too hard and do not collapse fully when applied to the mucous membrane of the eye, thus involving difficulties in the release of the ophthalmic drug from the gel, in the adsorption of the drug by the mucous membrane and in the absorption of the drug by the body.

The gel preparations of the present invention have a viscosity of from 1,000 to 100,000 centipoises. Preparations with a relatively low viscosity of from 1,000 to 10,000 centipoises have a good flowability and can be applied dropwise directly on to the mucous membrane around the eyeball. On the other hand, relatively viscous preparations having a viscosity of from 10,000 to 100,000 centipoises are less flowable and are pasty with the consistency of an ointment and can, therefore, be applied to the eyelids like conventional ophthalmic ointments to obtain the desired medicinal effect.

When the ophthalmic preparations of the present invention are applied, the tears liquefy the gel to give a liquid which can be readily adsorbed by the mucous membrane and cornea. Even viscous gels become liquid upon application due to a rapid reduction in viscosity so that the ophthalmic drug contained in the gel will be absorbed by the mucous membrane of the eye and the cornea in intimate contact therewith. Whereas conventional eye lotions are likely to be washed away by tears, the compositions

of the present invention are in the form of a gel which breaks down to ensure the adsorption of the ophthalmic drug on the mucous membrane of the eye or the like. Accordingly, the compositions can produce sufficient medicinal effects without being washed away by tears. Conventional ophthalmic ointments which contain petroleum jelly, lanolin or like oleophilic base ingredient are not intimately attached to the mucous membrane of the eye, are very likely to be washed away by tears without allowing sufficient absorption of the ophthalmic drug and give a sticky and uncomfortable feel to the eyelids. In contradistinction thereto, the ophthalmic compositions of the present invention, even when viscous, can be very easily converted by tears into a liquid which intimately attaches to the membrane. Furthermore, the new compositions cause no discomfort to the patient since they are free from oleophilic base ingredients. In the case of gel compositions of low viscosity, the mucous membrane of the eye intimately adsorbs and absorbs the ophthalmic drug rapidly, whereas a gel composition of higher viscosity takes a longer time for breakdown, resulting in moderate absorption of the drug and affording a sustained medicinal efficacy. For this reason, a gel composition of relatively low viscosity is preferable when it is desired to achieve a rapid medicinal effect by efficient adsorption on the mucous membrane, whereas a sustained efficacy is available for a prolonged period of time with a gel composition of relatively high viscosity. The viscosity, although somewhat dependent on the drug used, is governed mainly by the concentration of the carboxyvinyl polymer. For the formulation of gel compositions of specified viscosity, the carboxyvinyl polymer is used in the form of an aqueous solution having a concentration of 0.05 to 5.0% by weight. When the addition of some ophthalmic drugs leads to too low a viscosity, the desired viscosity can be obtained with use of an aqueous solution containing an increased amount of carboxyvinyl polymer.

The compositions of the present invention, when applied to the eye, undergo a marked reduction in viscosity, with a breakdown of the gel form, presumably due to the presence of sodium chloride in tears. We have found that the addition of a small amount of sodium chloride or of an aqueous solution thereof to the ophthalmic compositions of the present invention converts the gel to a liquid with a great reduction of its viscosity. However, we have found that the addition of a small amount of sodium chloride to the ophthalmic compositions of the present invention delays the breakdown of the gel when the compositions are applied to the mucous membrane of the eye. Thus, ophthalmic preparations containing sodium chloride are preferred when sustained efficacies are desirable. In this case, it is preferable to use an increased amount of carboxyvinyl polymer to compensate for the reduction of viscosity due to the addition of sodium chloride.

Although dependent upon the kind of ophthalmic drug incorporated, the compositions of the present invention, when containing steroids or antibiotics for example, are remarkably effective for curing various inflammatory diseases of the eye, such as keratitis,

scleritis, blepharitis and iridocyclitis. They are also useful for asthenopia (fatigue of the eyes), conjunctival injection (bloodshot eyes), prevention of ophthalmic diseases (after swimming or when dust or perspiration has got into the eye), inflammation of the eyes (snow blindness) caused by exposure to ultra-violet rays or other rays, dacryocystitis (watery eyes), inflammation of the eyelids (bleary eye), bacterial conjunctivitis, replenishment of tears and various other applications.

The following Examples are given for the purpose of illustrating the present invention; the viscosities were measured at 20°C. with a C-type viscosimeter produced by Tokyo Keiko Co. Ltd., Japan:—

15 *Example 1.*

1 g. Carboxyvinyl polymer ("Carbopol" 940) was dissolved in 99 g. sterilised and purified water to give a 1% aqueous solution of carboxyvinyl polymer. To 7.5 g. of this 1% aqueous solution of carboxyvinyl polymer were added 90.5 g. sterilised and purified water and 1.5 g. of a solution prepared by dissolving 2 g. sodium hydroxide in 98 g. sterilised and purified water was slowly added to the mixture, with good stirring. Upon continued stirring, the solution gelled. 0.5 g. Chloramphenicol powder was added thereto and the mixture was vigorously stirred to give a composition in the form of a gel containing 0.5% by weight of chloramphenicol uniformly dispersed therein and having a pH of 7.0 and a viscosity of 2,000 centipoises.

Example 2.

To a mixture of 20 g. of a 4% by weight aqueous solution of carboxyvinyl polymer and 74.8 g. sterilised and purified water were added 3.2 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring. When thoroughly stirred, the mixture gave a uniform gel to which 2 g. chloramphenicol powder were added. The resulting mixture was vigorously stirred to give a gel composition containing 2% by weight chloramphenicol and having a pH of 6.95 and a viscosity of 40,000 centipoises.

Example 3.

10 g. of a 1% aqueous solution of carboxyvinyl polymer were added to an aqueous solution of 0.02 g. water-soluble azulene (active component of camomile flowers) in 87.98 g. sterilised and purified water. To the mixture were added 2.0 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 7.00 and a viscosity of 4,000 centipoises.

Example 4.

0.05 g. Acrinol was dissolved in 82.79 g. sterilised and purified water, while heating on a water-bath, whereafter the solution was cooled. To the solution were added 14.3 g. of a 1% by weight aqueous solution of carboxyvinyl polymer and the mixture was stirred. Subsequently, 2.86 g. of a 2% by weight aqueous solution of sodium hydroxide were added to the mixture. The resulting mixture was thoroughly stirred to give a gel composition having a pH of 6.50 and a viscosity of 3,000 centipoises.

Example 5.

2 g. Boric acid were dissolved in 80.84 g. sterilised and purified water, while heating on a waterbath, whereafter the solution was cooled. To this solution

14.3 g. of a 1% by weight aqueous solution of carboxyvinyl polymer were added and the mixture was stirred. 2.86 g. of a 2% by weight aqueous solution of sodium hydroxide were then added to the mixture. The resulting mixture was thoroughly stirred to give a gel composition having a pH of 6.50 and a viscosity of 3,000 centipoises.

Example 6.

In 20 g. propylene glycol, heated to about 70°C. on a water-bath, were dissolved 0.05 g. of the butyric acid ester of riboflavin, whereafter the resulting solution was cooled. To this solution were added 67.09 g. sterilised and purified water and 10 g. of a 1% by weight aqueous solution of carboxyvinyl polymer and the mixture was thoroughly stirred. 2.86 g. of a 2% by weight aqueous solution of sodium hydroxide were then added to the mixture. The resulting mixture was thoroughly stirred to give a gel composition having a pH of 8.00 and a viscosity of 5,000 centipoises.

Example 7.

In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.1 g. of the butyric acid ester of riboflavin and the resulting solution was cooled. To this solution were added 50.9 g. sterilised and purified water, 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer and 4 g. of a 10% by weight aqueous solution of sodium hydroxide and the resulting mixture was thoroughly stirred to give a gel composition having a pH of 6.99 and a viscosity of 50,000 centipoises.

Example 8.

In 25 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.5 g. prednisolone and 60.1 g. sterilised and purified water and 12 g. of a 1% by weight aqueous solution of carboxyvinyl polymer added thereto. To the mixture were added 2.4 g. sodium hydroxide, with stirring, to give a gel composition having a pH of 7.10 and a viscosity of 2,200 centipoises.

Example 9.

In 20 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.5 g. prednisolone and 50.5 g. sterilised and purified water and 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added thereto. To the mixture were added 4 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 6.80 and a viscosity of 43,000 centipoises.

115 *Example 10.*

In 25 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.5 g. hydrocortisone and 60.1 g. sterilised and purified water and 12 g. of a 1% by weight aqueous solution of carboxyvinyl polymer were added thereto, with stirring. To the mixture were added 2.4 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 7.10 and a viscosity of 2,200 centipoises.

125 *Example 11.*

In 20 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.5 g. hydrocortisone and 50.5 g. sterilised and purified water and 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer added thereto, with stirring. To this mixture

were added 4 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 6.80 and a viscosity of 42,000 centipoises.

5 *Example 12.*

In 25 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.1 g. dexamethasone and 60.5 g. sterilised and purified water and 12 g. of a 1% by weight aqueous solution of carboxyvinyl polymer were added thereto, with stirring. To the mixture were added 2.4 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 7.05 and a viscosity of 2,200 centipoises.

15 *Example 13.*

0.1 g. Allantoin was dissolved in 76.7 g. sterilised and purified water, with warming, and to this solution were added 20 g. of a 4% by weight aqueous solution of carboxyvinyl polymer and 3.2 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 6.95 and a viscosity of 40,000 centipoises.

Example 14.

0.1 g. Allantoin was dissolved in 90.9 g. sterilised and purified water, with warming, and to this solution were added 7.5 g. of a 1% by weight aqueous solution of carboxyvinyl polymer and 1.5 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 15.

In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.05 g. flavine adenine dinucleotide and the resulting solution was cooled. To this solution were added 67.09 g. sterilised and purified water and 10 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with stirring. To this mixture were added 2.86 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 7.00 and a viscosity of 5,000 centipoises.

Example 16.

In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.1 g. flavine adenine dinucleotide and the resulting solution was cooled. To this solution were added 50.9 g. sterilised and purified water and 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. To this mixture were added 4 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring, to give a gel composition having a pH of 6.99 and a viscosity of 50,000 centipoises.

Example 17.

2.0 g. Boric acid were dissolved in 64.4 g. sterilised and purified water, with warming. After cooling, 12 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added to the solution, with stirring. To this mixture were added 9.6 g. of a 2% by weight aqueous solution of sodium hydroxide in small portions to give a gel composition having a pH of 6.90 and a viscosity of 30,000 centipoises.

To the above gel were added 12 g. of a 1% by weight aqueous solution of sodium chloride in small portions, with stirring. The viscosity of the gel decreased. After stirring thoroughly, a gel composition

was obtained having a pH of 7.00 and a viscosity of 3,000 centipoises.

Example 18.

In 25 g. propylene glycol, heated to about 90°C. on a water-bath, was dissolved 0.5 g. prednisolone and to the resulting solution were added 43 g. sterilised and purified water and 11.5 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. To this solution were added 8 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring. A uniform gel having a pH of 6.90 and a viscosity of 33,000 centipoises was obtained.

Subsequently, 12 g. of a 1% by weight aqueous solution of sodium chloride were added in small portions to the above gel, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,200 centipoises.

Example 19.

To 61.7 g. sterilised and purified water were added 11 g. of a 4% by weight solution of carboxyvinyl polymer, with stirring, and subsequently 8.8 g. of a 2% by weight aqueous solution of sodium hydroxide were added in small portions with thorough stirring to give a gel base having a pH of 6.90 and a viscosity of 29,000 centipoises.

To the above gel base were added 18 g. of a 1% by weight aqueous solution of sodium chloride in small portions, with stirring. The viscosity of the gel base decreased markedly due to the addition of the aqueous solution of sodium chloride. 0.5 g. Chloramphenicol powder was added to the above gel, with stirring, to give a uniform gel preparation having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 20.

0.02 g. Water-soluble azulene was dissolved in 47.28 g. sterilised water and to this solution were added 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring, and then 29.7 g. of a 2% by weight aqueous solution of triethanolamine were added in small portions, with stirring, to give a uniform gel having a pH of 6.90 and a viscosity of 28,000 centipoises.

12 g. of a 1% by weight aqueous sodium chloride solution were added in small portions, with stirring, to the above gel to give a uniform gel composition having a pH of 7.00 and a viscosity of 3,000 centipoises.

Example 21.

0.02 g. Vitamin B₁₂ was dissolved in 90.98 g. sterilised and purified water and to this solution were added 7.5 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with stirring. Subsequently, 1.5 g. of a 2% by weight aqueous solution of sodium hydroxide was added to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 22.

0.02 g. Vitamin B₁₂ was dissolved in 89.28 g. sterilised and purified water and to this solution were added 7.5 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. Subsequently, 3.2 g. of a 10% by weight aqueous solution of sodium hydroxide were added in small portions, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 40,000 centipoises.

Example 23.

- 0.1 g. Allantoin was dissolved in 87.3 g. sterilised and purified water, with stirring, and to this solution were added 7.5 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with stirring, and subsequently 5.1 g. of a 2% by weight aqueous solution of triethanolamine was added in small portions, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 24.

- 0.1 g. Allantoin was dissolved in 53.5 g. sterilised and purified water, with warming. To this solution were added 20 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring, and subsequently 26.4 g. of a 2% by weight aqueous solution of triethanolamine were added in small portions, with stirring, to give a uniform gel composition having a pH of 6.95 and a viscosity of 40,000 centipoises.

Example 25.

- In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.05 g. flavine adenine dinucleotide and the solution then cooled. To this solution were added 66.65 g. sterilised and purified water and 10 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with stirring, to give a uniform solution. 3.3 g. of a 2% by weight aqueous solution of monoethanolamine were added in small portions to the above solution, to give a uniform gel composition having a pH of 7.00 and a viscosity of 5,000 centipoises.

Example 26.

- In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.1 g. flavine adenine dinucleotide and the solution then cooled. To this solution were added 21.9 g. sterilised and purified water and 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring, to give a uniform solution. 3.3 g. of a 2% by weight aqueous solution of monoethanolamine were added, with stirring, in small portions to the above solution to give a uniform gel composition having a pH of 6.99 and a viscosity of 50,000 centipoises.

Example 27.

- 0.02 g. Water-soluble azulene was dissolved in 83.23 g. sterilised and purified water. To this solution were added 10 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with stirring, and subsequently 6.75 g. of a 2% by weight aqueous solution of triethanolamine were added in small portions, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 4,000 centipoises.

Example 28.

- In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.05 g. of the butyric acid ester of riboflavin and the solution then cooled. To this solution were added 66.65 g. sterilised and purified water and 10 g. of a 1% by weight aqueous solution of carboxyvinyl polymer were added, with stirring, and then 3.3 g. of a 2% by weight aqueous solution of monoethanolamine were added in small portions, with stirring, to give a uniform gel composition having a pH of 8.00 and a viscosity of 5,200 centipoises.

Example 29.

- 0.02 g. Vitamin B₁₂ was dissolved in 62.18 g. sterilised and purified water and to this solution were

added 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. Subsequently, 8.8 g. of a 2% by weight aqueous solution of sodium hydroxide were added in small portions to the above mixture to give a uniform gel having a pH of 6.90 and a viscosity of 29,000 centipoises.

- To the above gel were added, with stirring, 18 g. of a 1% by weight aqueous solution of sodium chloride in small portions to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 30.

- 0.1 g. Allantoin was dissolved in 43.2 g. sterilised water, with warming. To this solution were added 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring, and subsequently 29.7 g. of a 2% by weight aqueous solution of triethanolamine were added, with stirring, to give a uniform gel having a pH of 6.90 and a viscosity of 28,000 centipoises.

- To the above gel were added, with stirring, 16 g. of a 1% by weight aqueous solution of sodium chloride in small portions to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 31.

- In 20 g. propylene glycol, heated to about 70°C. on a water-bath, was dissolved 0.05 g. flavine adenine dinucleotide. After cooling the solution, 41.95 g. sterilised and purified water and 12 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added, with stirring, and then 16 g. of a 2% by weight aqueous solution of monoethanolamine were added in small portions to give a uniform gel having a pH of 6.80 and a viscosity of 34,000 centipoises.

- To the above gel were added, with stirring, 10 g. of a 1% by weight aqueous solution of sodium chloride, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 5,000 centipoises.

Example 32.

- 2 g. Boric acid were dissolved in 83.96 g. sterilised and purified water, with warming on a water-bath. After cooling, 12 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added to the above solution, with stirring, and then 1.92 g. of a 10% by weight aqueous solution of sodium hydroxide was added in small portions, with stirring, to give a uniform gel.

- To the above gel was added 0.12 g. sodium chloride in small portions, the viscosity of the gel decreasing markedly. Stirring was continued to give a uniform gel composition having a pH of 7.00 and a viscosity of 3,000 centipoises.

Example 33.

- In 25 g. propylene glycol, heated to about 90°C., was dissolved 0.5 g. prednisolone and then 61.28 g. sterilised and purified water and 11.5 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added, with stirring.

- To the above solution was added 1.6 g. of a 10% by weight aqueous solution of sodium hydroxide in small portions, with stirring, to give a uniform gel. To this gel was added 0.12 g. sodium chloride, with

stirring, in small portions to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,200 centipoises.

Example 34.

- 5 To a mixture of 86.56 g. sterilised and purified water and 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer was added 1.76 g. of a 10% by weight aqueous solution of sodium hydroxide, with stirring, to give a uniform gel. 0.18 g. Sodium chloride was then added in small portions, with stirring, to decrease the viscosity. Subsequently, 0.5 g. chloramphenicol powder was added to the above gel and the mixture thoroughly stirred to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 35.

- 0.02 g. Water-soluble azulene was dissolved in 87.1 g. sterilised and purified water. To this solution were added 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. Subsequently, 1.76 g. of a 10% by weight aqueous solution of sodium hydroxide was added in small portions, with stirring, to give a uniform gel.

- To the above gel was added 0.12 g. sodium chloride in small portions to decrease the viscosity and to give a uniform gel composition having a pH of 7.00 and a viscosity of 4,000 centipoises.

Example 36.

- Allantoin was dissolved in 86.46 g. sterilised and purified water and to this solution were added 11 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring, and 1.76 g. of a 10% by weight aqueous solution of sodium hydroxide was added in small portions, with thorough stirring, to give a uniform gel. Subsequently, while stirring the above gel, 0.18 g. sodium chloride was added in small portions to decrease the viscosity of the gel and to give a uniform gel composition having a pH of 7.00 and a viscosity of 2,000 centipoises.

Example 37.

- In 20 g. propylene glycol, heated to about 70°C., was dissolved 0.05 g. flavine adenine dinucleotide. After cooling, 66.06 g. sterilised and purified water and 12 g. of a 4% by weight aqueous solution of carboxyvinyl polymer were added to the above solution and 1.8 g. of a 10% by weight aqueous solution of sodium hydroxide was added in small portions, with stirring, to give a uniform gel. 0.09 g. Sodium chloride was then added in small portions, with stirring, to give a uniform gel composition having a pH of 7.00 and a viscosity of 5,000 centipoises.

Example 38.

- In 25 g. propylene glycol, heated to about 90°C., was dissolved 0.05 g. fluocinonide. To this solution were added 60.55 g. sterilised and purified water and 12 g. of a 1% by weight aqueous solution of carboxyvinyl polymer, with thorough stirring. 2.4 g. of a 2% by weight aqueous solution of sodium hydroxide were then added, with stirring, to the above solution giving a gel composition having a pH of 6.70 and a viscosity of 3,400 centipoises.

Example 39.

- In 25 g. propylene glycol, heated to about 90°C., were dissolved 0.05 g. fluocinonide. To this solution were added 43.45 g. sterilised and purified water and

- 11.5 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with stirring. To this solution were added 8 g. of a 2% by weight aqueous solution of sodium hydroxide, with stirring, to give a uniform gel having a pH of 6.92 and a viscosity of 33,000 centipoises.

- Subsequently, 12 g. of a 1% by weight aqueous solution of sodium chloride were added in small portions to the above gel, with stirring, to give a uniform gel composition having a pH of 6.96 and a viscosity of 2,000 centipoises.

Example 40.

- In 25 g. propylene glycol, heated to about 90°C., was dissolved 0.05 g. fluocinonide. To this solution were added 45.95 g. sterilised and purified water and 25 g. of a 4% by weight aqueous solution of carboxyvinyl polymer, with thorough stirring. 4 g. of a 10% by weight aqueous solution of sodium hydroxide were added to the above solution, with thorough stirring, to give a gel composition having a pH of 6.75 and a viscosity of 41,000 centipoises.

CLAIMS

1. An ophthalmic composition in the form of a gel comprising an aqueous solution of a carboxyvinyl polymer, a water-soluble basic substance and an ophthalmic drug admixed therewith, the gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

2. An ophthalmic composition according to claim 1, wherein sodium chloride is incorporated therein.

3. Ophthalmic composition according to claim 1, substantially as hereinbefore described and exemplified.

4. A process for preparing an ophthalmic composition according to claim 1, wherein an aqueous solution of a carboxyvinyl polymer is uniformly mixed with a water-soluble basic substance and an ophthalmic drug is added to the solution to give a gel having a pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

5. A process according to claim 4, wherein the ophthalmic drug is dissolved or dispersed in the aqueous carboxyvinyl polymer solution and the resulting solution or dispersion is uniformly mixed with the water-soluble basic substance.

6. A process according to claim 4, wherein the aqueous carboxyvinyl polymer solution is uniformly mixed with the water-soluble basic substance and the resulting mixture is uniformly mixed with the ophthalmic drug or with a solution thereof.

7. A process according to any of claims 4 to 6, wherein the aqueous carboxyvinyl polymer solution contains 0.05 to 5.0% by weight of the carboxyvinyl polymer.

8. A process for preparing an ophthalmic composition according to claim 1, wherein sodium chloride or an aqueous solution thereof is added to an aqueous solution of a carboxyvinyl polymer or to a base composition in the form of a gel prepared by adding a water-soluble basic substance to the polymer solution or to an ophthalmic composition in the form of a gel prepared by adding an ophthalmic drug to the base composition, followed by uniformly mixing the resulting mixture to give a gel having a

pH of 5 to 8 and a viscosity of 1,000 centipoises to 100,000 centipoises at 20°C.

9. A process according to any of claims 4 to 8, wherein the water-soluble basic substance is an
5 alkylamine, dialkylamine, trialkylamine, alkanolamine, dialkanolamine, trialkanolamine, trimethylolaminomethane, alkali metal hydroxide or ammonia.

10. A process for preparing an ophthalmic composition according to claim 1, substantially as
10 hereinbefore described and exemplified.

11. Ophthalmic compositions, whenever prepared by the process according to any of claims 4 to 10.

Printed for Her Majesty's Stationery Office by The Tweeddale Press Ltd.,
Berwick-upon-Tweed, 1979.
Published at the Patent Office, 25 Southampton Buildings, London, WC2A 1AY,
from which copies may be obtained.